Glucagon vs. Insulin

Introduction

This lesson explores various reactions in metabolism and how they relate to each of the five cells. Again, don't commit to memorizing the details of the reactions. Rather, get a feel for which cells do what, and how hormones influence their function. This is also an overview of the reactions we'll study in the course.

Glycolysis, pyruvate dehydrogenase, citric acid cycle, electron transport chain, glycogen storage and utilization, fatty acid synthesis, fatty acid oxidation, ketone synthesis, ketone catabolism, and a touch of amino acid metabolism…sounds like a lot. It is.

We use "oxidative phosphorylation" and "TCA-ETC" interchangeably so you get used to the idea that they are the same thing. Glycolysis and pyruvate dehydrogenase go together and make acetyl-CoA. There are other ways to get to acetyl-CoA. Once at acetyl-CoA, the Krebs cycle (TCA) produces NADH and $FADH_2$ for the electron transport chain (ETC) to make ATP.

Hormone Balance

The pancreas is responsible for sensing the **whole-body state** of blood glucose. If the whole-body glucose is high, **insulin is released**. If the whole-body glucose is low, **glucagon is released**. Every cell receives this one message from the pancreas. Some cells respond more vigorously to these signals—the liver changes everything it does based on insulin or glucagon. Some cells respond very little to these signals—neurons keep using glucose regardless.

Five Cells of Metabolism

RBCs have no mitochondria. They can perform only glycolysis, and only the anaerobic variant.

Brain cells have mitochondria, but no downtime. They can utilize glucose through glycolysis, and also amplify ATP using oxidative phosphorylation. Ketone bodies, fatty acid oxidation, and glycogen can't be used.

Skeletal muscle cells have mitochondria and downtime, and can process amino acids. They can utilize glucose through glycolysis, amplify ATP using oxidative phosphorylation, use ketones, use fatty acids, and build and use glycogen.

Adipose cells are special. They use glucose for ATP through oxidative phosphorylation, but mostly store triglycerides from the liver and mobilize them back to the liver.

Liver cells do everything except use ketones. Liver is the only cell that can synthesize glucose or ketones for the other cells.

Superficial Look at the Hormone Balance: Insulin Dominant

The **default** of all cells is to use glucose. "Use glucose" means glycolysis, pyruvate dehydrogenase, Krebs cycle (TCA), and/or electronic transport chain. When glucose is abundant, all cells use that glucose. They use it to increase their own energy stores (NADH, $FADH_2$, and ultimately ATP). Then, once they have enough energy, those that can store it away do just that. Energy is stored as **glycogen** (skeletal muscle, adipose, hepatocytes), as **protein** in skeletal muscle, and as **triglycerides** in adipose—synthesized in and dispatched from the liver.

CELL TYPE	WHAT IT'S DOING METABOLICALLY	HOW IT CONTRIBUTES
RBC	Burns glucose, anaerobic	N/A
Brain	Burns glucose	N/A
Skeletal muscle	Burns glucose **Builds glycogen**	**Stores** amino acids
Adipose	Burns glucose **Builds glycogen**	**Stores** triglycerides from liver
Hepatocytes	**Burns glucose**	**Builds fatty acids** (to adipose)

Table 2.1: The Five Cells in the Insulin-Dominant State
A superficial look at the different cell types and what they do when the body is in the insulin-dominant state.

RBCs are anaerobic, lacking metabolism. They never change. Brain cells are so metabolically active, that while they do have mitochondria, they never store energy for later. Like RBCs, they just keep doing what they're doing.

Superficial Look at the Hormone Balance: Glucagon Dominant

Glucagon predominates in someone not engaged in eating. That is, as caloric intake drops off, so do the blood sugars. The pancreas senses this change, stops the production of insulin, and turns on glucagon. This changes the dynamics of the system, but a lot less than you'd think.

Fat sends triglycerides back to the liver. Skeletal muscle sends amino acids back to the liver. The tissues with glycogen stores can use glycogen. The liver makes energy for other cells to use—be it glucose or ketone bodies. Different tissues will prefer glucose or ketone bodies (now is not the time to learn which one prefers which).

CELL TYPE	WHAT IT'S DOING METABOLICALLY	HOW IT CONTRIBUTES
RBC	Burns glucose, anaerobic	N/A
Brain	Burns glucose	N/A
Skeletal muscle	Burns glucose **and glycogen**	**Mobilizes** amino acids for liver
Adipose	Burns glucose **and glycogen**	**Mobilizes** triglycerides for liver
Hepatocytes	**Burns fatty acids** (from adipose) **Burns amino acids** (from muscle)	**Builds glucose** **Builds ketone bodies**

Table 2.2: The Five Cells in the Glucagon-Dominant State
A superficial look at the different cell types and what they do when the body is in the glucagon-dominant state.

Insulin-Dominant State: Detail by Cell

Red blood cells only know how to do one thing: glycolysis. So, they continue to do their one thing: glycolysis. The only difference is that the glucose the RBCs use in the **insulin-dominant state** is from **the diet**, whereas the glucose the RBCs use in the **glucagon-dominant state** is from the **liver**. Red blood cells have no mitochondria. That means they can't do any of the glucose-burning stuff that makes a lot of ATP. That translates to no pyruvate dehydrogenase, citric acid cycle, or electron transport chain. It also means that they must rely on **lactate** and the liver to recycle that lactate back into glucose. This is called the **Cori cycle**. Red blood cells are the easiest. All they have is **glycolysis**.

Brain cells only know how to do two things: glycolysis and oxidative phosphorylation. Brain cells have **mitochondria**. They are just like red blood cells in that all they know how to do is burn glucose. "Burning" in the brain cells consists of **oxidative phosphorylation**, glycolysis, pyruvate dehydrogenase, then TCA-ETC. The only difference between insulin-dominant glucose and glucagon-dominant is that insulin-dominant glucose comes from the diet, and glucagon-dominant glucose comes from the liver. It is possible for the brain to use ketone bodies, but only after a prolonged starvation in severe and nonphysiological conditions—it can, but usually doesn't.

Skeletal muscle starts to get more complicated. Skeletal muscle has the job of contracting. Skeletal muscle, when it's needed, needs to do a lot of work in a short amount of time. A contraction requires a lot of ATP. And then between contractions, very little is needed. This is why skeletal muscle has **glycogen**. Skeletal muscle has **mitochondria**, which means that oxidative phosphorylation (pyruvate dehydrogenase, TCA-ETC) of glucose is what skeletal muscle does under the influence of insulin. That glucose comes from the diet in the insulin-dominant state. But once the cell is flush with energy (immediate use), **insulin stimulates skeletal muscle to make glycogen**. Glycogen is glucose stored within the cell. When energy is needed for contraction, it will be ready. In the insulin-dominant state, skeletal muscle cells are using glucose, and so we mentioned only glucose (see later).

Adipose cells have similarities, but things get a little harder. Adipose cells have mitochondria, which means they will burn glucose under oxidative phosphorylation. But one of the products of glycolysis can also become the 3-carbon sugar **glycerol-3-p**, which makes up the backbone for triglycerides. The adipose cells will make sure they have enough immediate energy, just like every other cell (pyruvate, TCA, ETC). But when flush, rather than storing sugar as glycogen, adipose tissue stores **fatty acids from the liver as triglycerides**. Same concept—default glycolysis-TCA-ETC to get ATP, then store energy—but different storage mechanism.

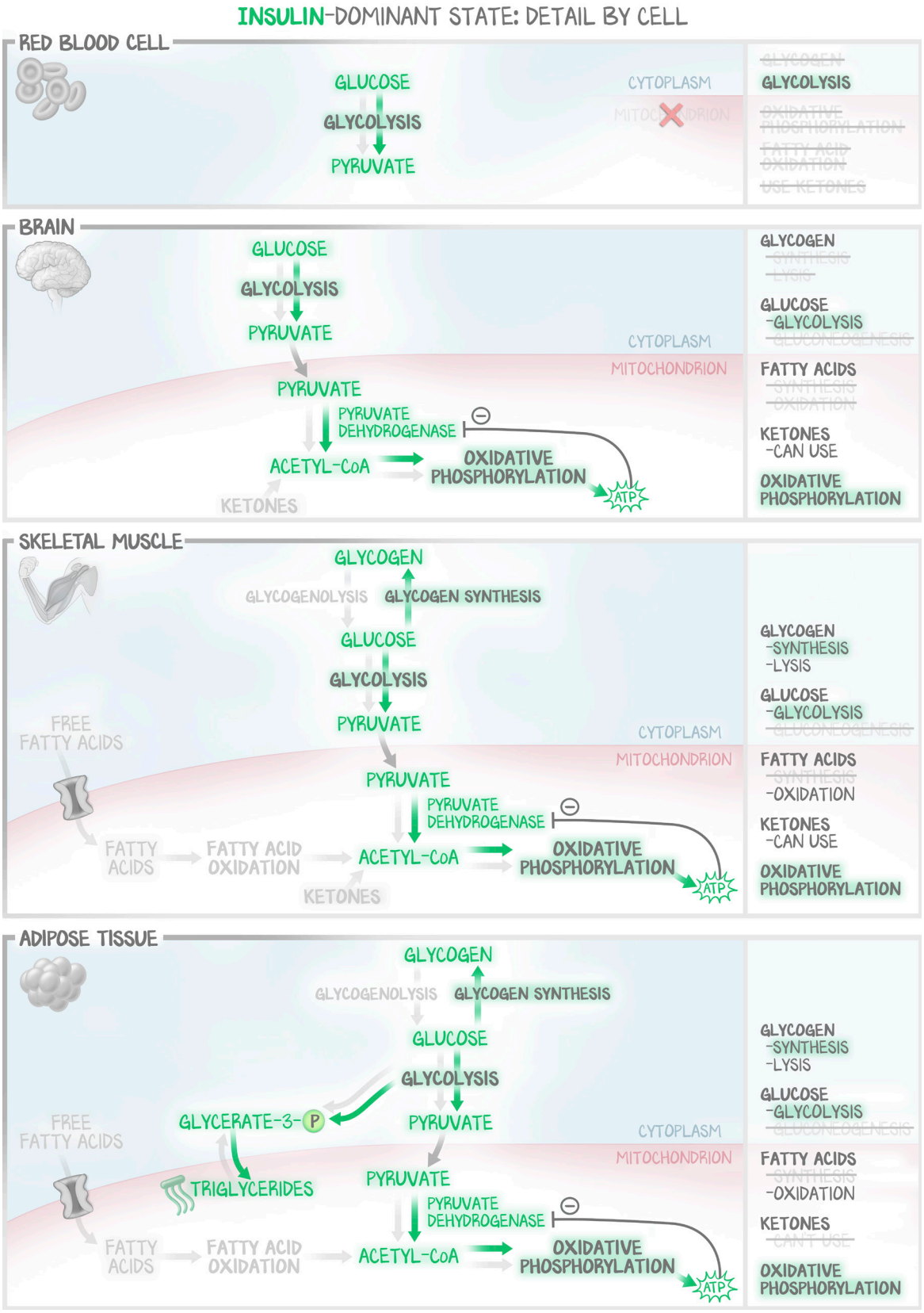

Figure 2.1: Insulin-Dominant State: Detail by Cell
A closer look at the metabolic pathways each cell utilizes in the insulin-dominant state.

The liver has mitochondria, so its default is glycolysis-TCA-ETC to energize itself. When has enough energy, it begins storing excess energy. In the **insulin-dominant state** the liver will **store glucose as glycogen** (like skeletal muscle) AND **make fatty acids to store as triglycerides in adipose**. Yes, the image looks really scary. But see how few global things are happening. It's the details that make this hard.

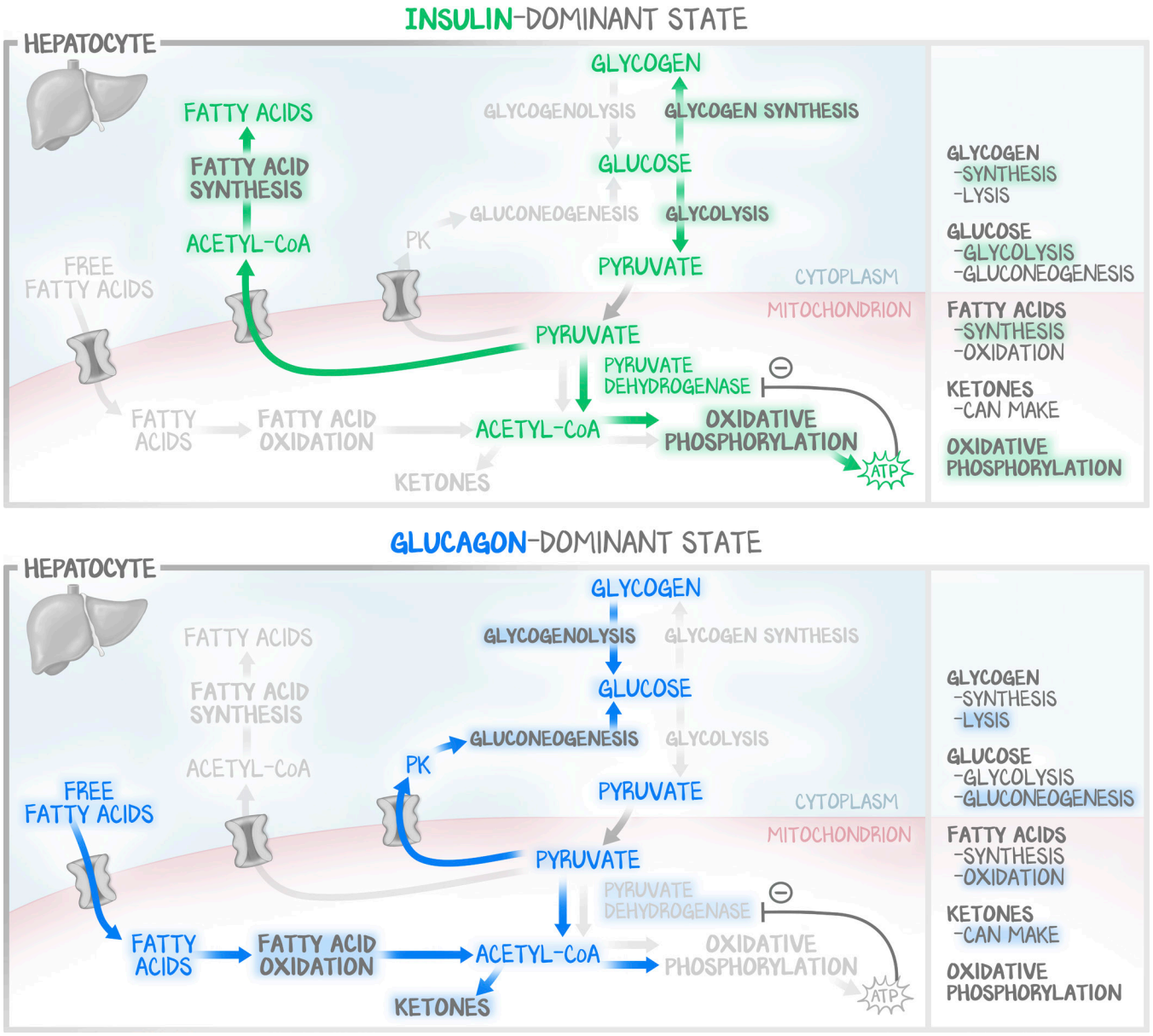

Figure 2.2: The Hepatocyte in Detail
A look at what the liver can do in both the insulin-dominant and glucagon-dominant state. We address the liver separately.

Glucagon-Dominant State: Detail by Cell

Red blood cells do nothing different; their glucose comes from the liver.

Brain cells do nothing different. Their glucose comes from the liver. When literally starving, brain cells can use ketone bodies, but they'd rather not. Even though there are mitochondria for TCA-ETC, brain cells don't have the machinery for fatty acid oxidation.

Skeletal muscle has a lot of skills, but its only real goal is to contract, so it makes energy for itself and uses the energy supplied by the liver. The most rapid access to glucose comes from **glycogenolysis**. That'll deplete quickly, so other mechanisms exist. The skeletal muscle has **mitochondria** and **does know how** to use **fatty acid oxidation** inside the skeletal muscle cell. Unlike the brain, **muscles like ketone bodies** (especially cardiac muscle). But ketones are only made when the liver has oxidized many fatty acids, gotten energy-rich itself, and starts producing ketone bodies as a product of fatty acid oxidation. It's fast, just not as fast as glycogenolysis.

Adipose has a directional shift. The adipose cell's job is to store triglycerides in the insulin-dominant state. It dedicated its glucose to glycerol-3-p to assemble triglycerides. Now, adipose will use **glycolysis** (now using hepatic glucose) to maintain a flush energy state. Adipose cells also know how to use the fatty acids they store to derive energy from **fatty acid oxidation**. The directional shift is towards the **dispatching of glycerol** (becomes glucose) and **fatty acids** (becomes acetyl-CoA) to the liver by breaking down triglycerides and sending all the pieces back to the liver.

In the glucagon-dominant state, the **liver** does the **opposite of whatever it did under insulin**. Glycolysis becomes gluconeogenesis. Glycogen storage becomes glycogenolysis. Fatty acid synthesis (cytoplasm) becomes fatty acid oxidation (mitochondria) and ketone formation. What **doesn't change** is the need for energy. The liver needs to take care of itself, make sure it has enough energy, so will still take advantage of TCA-ETC. But the acetyl-CoA used for TCA-ETC comes now from **fatty acid oxidation** rather than glycolysis and pyruvate dehydrogenase. All sugars are instead diverted to **gluconeogenesis rather than glycolysis**.

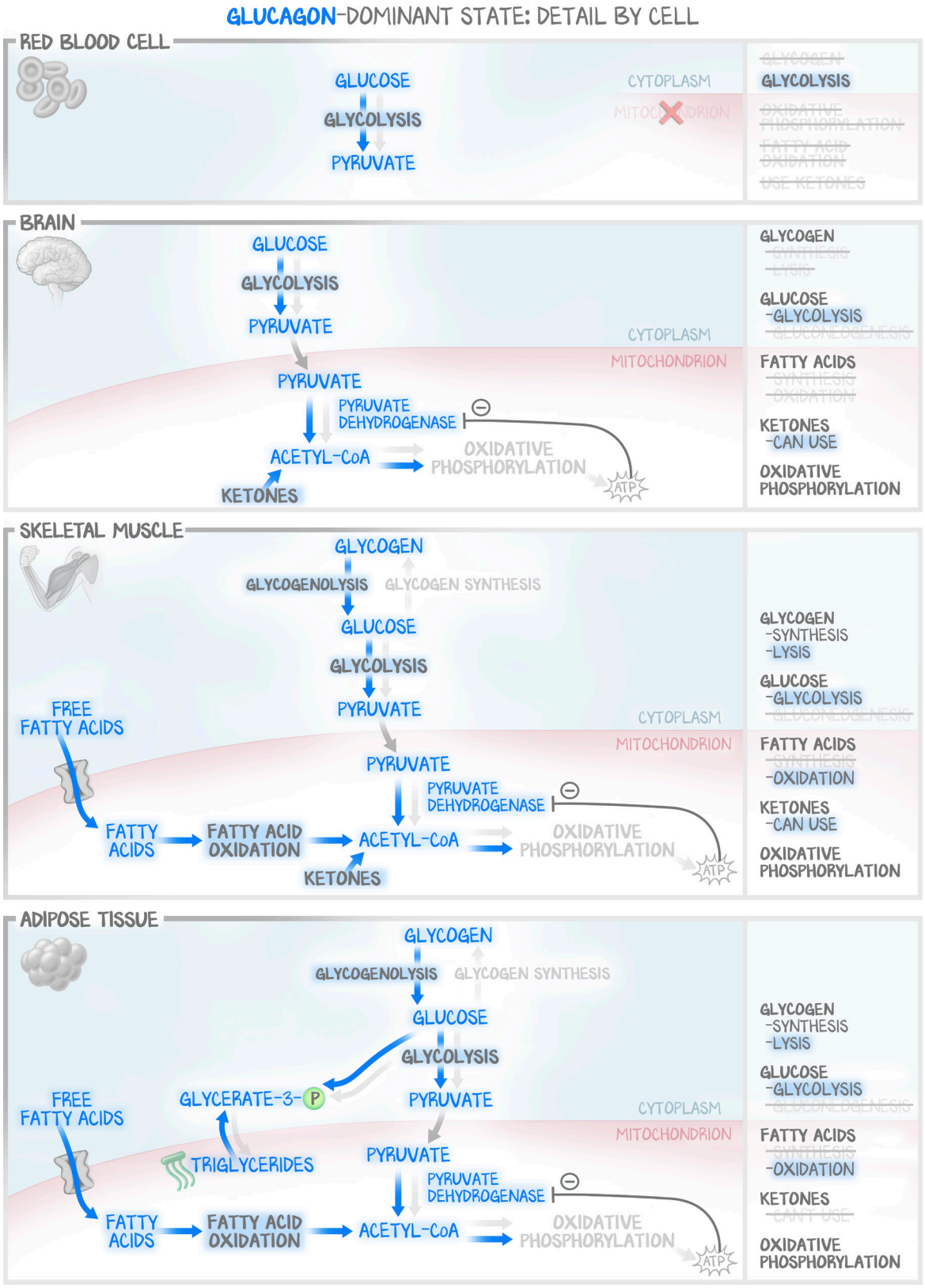

Figure 2.3: Glucagon-Dominant State: Detail by Cell
A closer look at the metabolic pathways each cell utilizes in the glucagon-dominant state.